

a.) Amendment to the Specification:

Please amend the paragraph starting at page 21, line 32 and ending at page 23, line 18 to read as follows.

Regarding the antibodies, any antibodies against antigens expressed in tumor cells or antigens involved in formation of tumor pathogenic states such as growth and metastasis of tumor cells may be used. Examples thereof include antibodies against interleukin-6 (IL-6) receptor, GD2, GD3, GM2, HER2, CD20, CD22, CD33, CD52, MAGE, HM1.24, parathyroid hormone-related protein (PTHrP), basic fibroblast growth factor, fibroblast growth factor 8, basic fibroblast growth factor receptor, ~~fibroblast growth factor 8 receptor~~ acidic fibroblast growth factor receptor, epithelial cell growth factor receptor (EGFR), epithelial cell adhesion molecule (EpCam), insulin-like growth factor, insulin-like growth factor receptor, PMSA, vascular endothelial cell growth factor (VEGF), vascular endothelial cell growth factor receptor (VEGFR) and the like.

Specific examples of the antibodies do not limit the scope of the invention. The anti-IL-6 receptor antibody includes those described in Anticancer Res., 18, 1217 (1998), the anti-GD2 antibody includes those described in Anticancer Res. 13, 331 (1993), the anti-GD3 antibody includes those described in Cancer Immunol. Immunother., 36, 260 (1993), the anti-GM2 antibody includes those described in Cancer Res., 54, 1511 (1994), the anti-HER2 antibody includes those described in Proc. Natl. Acad. Sci. USA, 89, 4285 (1992), the anti-CD20 antibody includes those described in Blood, 83, 435 (1994), the anti-CD22 antibody includes those described in Semmin. Oncol., 30, 253 (2003), the anti-CD33 antibody includes those described in J. Clin. Oncol., 19, 3244 (2001), the anti-CD52 antibody includes those described in Proc. Natl. Acad. Sci. USA, 89, 4285 (1992), the

anti-MAGE antibody includes those described in British J. Cancer, 83, 493 (2000), the anti-HM1.24 antibody includes those described in Molecular Immunol., 36, 387 (1999), the anti-parathyroid hormone-related protein (PTHrP) antibody includes those described in Cancer, 88, 2909 (2000), the ~~anti-fibroblast growth factor 8 antibody~~ anti-acidic fibroblast growth factor antibody includes those described in Proc. Natl. Acad. Sci. USA, 86, 9911 (1989), the anti-fibroblast growth factor 8 receptor antibody includes those described in J. Biol. Chem., 265, 16455 (1990), the anti-epidermal cell growth factor receptor antibody includes those described in Cancer Res., 59, 1236 (1999), the anti-epidermal cell adhesion molecule antibody includes those described in Proc. Natl. Acad. Sci. USA, 76, 1438 (1979), the anti-insulin-like growth factor antibody includes those described in J. Neurosci. Res., 40, 647 (1995), the anti-insulin-like growth factor receptor antibody includes those described in J. Neurosci. Res. 40, 647 (1995), the anti-PMSA antibody includes those described in J. Urology, 160, 2396 (1998), the anti-vascular endothelial cell growth factor antibody includes those described in Cancer Res. 57, 4593 (1997), and the anti-vascular endothelial cell growth factor receptor antibody includes those described in Oncogene, 19, 2138 (2000).

Please amend the paragraph at page 54, lines 6-7 to read as follows.

Examination of an effect provided by using irradiation and an ~~anti-IGF-I~~
anti-IGF monoclonal antibody in combination

Please amend the paragraphs at page 55, lines 6-16 to read as follows.

In comparison to no X-ray irradiation, X-ray irradiation decreased the number of colonies to approximately 50%. The addition of anti-IGF monoclonal antibody KM 1468 decreased the number of colonies to 20% or less. In view of the foregoing, it has been confirmed that the combined use of irradiation and the ~~anti-IGF-I~~ anti-IGF monoclonal antibody is useful for treating cancer.

(Example 2)

Examination of an effect provided by using an agent having low-molecular weight and an ~~anti-IGF-I~~ anti-IGF monoclonal antibody in combination

Please amend the paragraph at page 56, lines 27-29 to read as follows.

Examination of an administration method in the combined use of a agent having low-molecular weight and an ~~anti-IGF-I~~ anti-IGF monoclonal antibody

Please amend the paragraph starting at page 64, line 1 and ending at page 65, line 9 to read as follows.

As shown in Reference Example 1(4), a plate where antigen was immobilized was prepared, each antibody diluted to 4.0 µg/mL was dispensed in an amount of 50 µL/well, then hIGF-I or hIGF-II diluted in a 3-fold dilution step from 20 µg/mL or human insulin or mIGF-I diluted in a 5-fold serial dilutions from 10 µg/mL was dispensed in an amount of 50 µL/well and they were mixed and reacted at room

temperature for 1 hour. After the reaction, it was washed with Tween-PBS and, in the case of KM 1468, a peroxidase-labeled rabbit anti-rat Ig antibody (manufactured by Dako) diluted to 4,000-fold or, in the case of sm1.2, a peroxidase-labeled rabbit anti-rat Ig antibody (manufactured by Dako) diluted to 2,000-fold was added in an amount of 50 μ L/well followed by reacting at room temperature for 1 hour. After the reaction, it was washed with Tween-PBS, 50 μ L/well of ABTS substrate solution [a solution prepared by dissolving 0.55 g of ammonium 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) in 1 L of 0.1 M citrate buffer (pH 4.2) following by adding with 1 μ L/ml of an aqueous solution of hydrogen peroxide immediately before use] was added thereto to effect color development and OD415 was measured using a plate reader Emax (manufactured by Molecular Devices). The result was given in terms of a relative value (%) where the OD415 when only antibody was added was defined as 100. The result was shown in Fig. 4. As shown in Fig. 4, binding of the antibody KM 1468 to hIGF-I was strongly inhibited by hIGF-I (Fig. 4A) and hIGF-II (Fig. 4B) and a 50% inhibition concentration (hereinafter, referred to as IC₅₀) for the binding by hIGF-I was about 0.3 μ g/mL (about 39 nM) while the IC₅₀ by hIGF-II was about 0.4 μ g/mL (about 58 nM) whereby they showed nearly the same value. On the other hand, no inhibition was noted in human insulin and mIGF-I. From the above result, it has been clarified that the antibody KM 1468 reacts with both hIGF-I and hIGF-II almost the same specificity and almost the same degree. Binding of sm1.2 which is the commercially available ~~anti-IGF-I~~ anti-IGF antibody to hIGF-I was strongly inhibited by hIGF-I (Fig. 4A) and an inhibitory activity by hIGF-II (Fig. 4B) was weak. IC₅₀ of sm1.2 by hIGF-I was about 1.2 μ g/mL (about 156 nM) while IC₅₀ by hIGF-

II was $>10\text{ }\mu\text{g/mL}$ ($> 1.45\text{ }\mu\text{M}$). On the other hand, no inhibition was noted in human insulin and mIGF-I.